

Novel Coronavirus Disease-19 and Host Immune Response: A Review

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ABSTRACT

As the world is witnessing the epidemic of coronavirus (CoV) disease-19, a disease caused by a novel CoV, severe acute respiratory syndrome CoV (SARS)-CoV-2, emerging genetics and clinical evidences suggest a similar path to those of SARS and Middle East respiratory syndrome. A cascade of viral particles enters the body through the nose, eyes, or mouth. Breathing carries some of these particles to the lower respiratory tract where the spike proteins of the CoV, acting like a key, lock into epithelial cells that line the respiratory tract as well as those in the air sacs in the lungs. SARS-CoV-2 is able to stay undetected longer than many flu or CoVs and its spike proteins are able to gain entry by unlocking the angiotensin-converting enzyme-2 (ACE2) protein on the lung cells. Once in, they hijack the cell's machinery, replicate and multiply and infect adjoining cells. Like the defining ACE2 proteins on the epithelial cells, viruses too have a tell-tale signature on their surface called antigens and spotting these is what kicks the immune system into action by producing antibodies. The paper was aimed to review the host immune response in relation to SARS-CoV-2.

Key words: Coronavirus, coronavirus disease-19, immune system, immune response

INTRODUCTION

The world experienced the outbreaks of coronavirus (CoV) infection that threatens global pandemic in 2002–2003 by severe acute respiratory syndrome (SARS) and in 2011 by Middle East respiratory syndrome (MERS). In both cases, the causative agents (SARS-CoV and MERS-CoV, respectively) were newly identified CoV in the genus beta CoV with zoonotic origin. At the end of 2019, outbreak of another CoV that causes respiratory-related illness was reported in Wuhan, Hubei, China, a disease now officially called “the CoV disease 2019 (COVID-19).” The CoV that is the causative agent of this respiratory disease was identified and its genome is fully sequenced.^[1]

According to disease progression, patients may be roughly divided into two groups; asymptomatic or mild cases that usually recover and severe cases (approximately 15%) that

develop multi organ failure, primarily respiratory failure, requiring intensive care unit (ICU) admission.^[2,3] An efficient immune response against SARS-CoV-2 may be considered fundamental for the resolution of COVID-19. However, some studies have shown a significant relationship between the disease severity and the levels of pro-inflammatory cytokines and subsets of immune cells.^[4,5] It has been suggested that during the response to SARS-CoV-2, the immune dysregulation and the high level of pro-inflammatory cytokines could be the main cause of tissue injury. Eventually, the exact pathophysiologic mechanism of COVID-19 remains still largely unknown.^[6]

CoVs

CoV are enveloped viruses with a positive sense single-stranded RNA genome (26e32 kb). Four CoV genera (α , β , γ , and δ) have been identified so far, with human CoVs

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(HCoV) detected in α CoV (HCoV-229E and NL63) and β CoV (MERS-CoV, SARS-CoV, HCoV-OC43, and HCoV-HKU1) genera.^[7] The genome of SARS-CoV-2 is similar to that of typical CoVs and contains at least ten open reading frames (ORFs). The first ORFs (ORF1a/b), about two-thirds of viral RNA, are translated into two large polyproteins. In SARS-CoV and MERS-CoV, two polyproteins, pp1a and pp1ab, are processed into 16 non-structural proteins (nsp1-nsp16), which form the viral replicase-transcriptase complex.^[8] Those nsps rearrange membranes originating from the rough endoplasmic reticulum into double-membrane vesicles where viral replication and transcription occur.^[9,10] The other ORFs of SARS-CoV-2 on the one-third of the genome encode four main structural proteins: Spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins as seen in Figure 1, as well as several accessory proteins with unknown functions which do not participate in viral replication.

PATHOGENESIS OF COV

Like the other respiratory CoVs, SARS-CoV-2 is transmitted primarily through respiratory droplets, with a possible, but unproven, fecal–oral transmission route. On infection, the median incubation period is approximately 4–5 days before symptom onset,^[3,11] with 97.5% of symptomatic patients developing symptoms within 11.5 days.^[12] At the point of hospital admission, patients with COVID-19 typically exhibit a fever and dry cough; less commonly, patients also experience difficulty in breathing, muscle and/or joint pain, headache/dizziness, diarrhea, nausea, and the coughing up of blood.^[3,13-15] Within 5–6 days of symptom onset, SARS-CoV-2 viral load reaches its peak – significantly earlier than that of the related SARS-CoV, where viral load peaks at about 10 days after symptom onset.^[16-18] Severe COVID-19 cases progress to acute respiratory distress syndrome (ARDS), on average around 8–9 days after symptom onset.^[2,14]

The pathophysiology of SARS-CoV-2 infection closely resembles that of SARS-CoV infection, with aggressive inflammatory responses strongly implicated in the resulting damage to the airways.^[19] Therefore, disease severity in patients is due to not only the viral infection but also the host response. The pattern of increasing severity with age is also broadly consistent with the epidemiology of SARS-CoV and MERS-CoV.^[14] ARDS seen in severe COVID-19 is characterized by difficulty in breathing and low blood oxygen level.^[20] As a result, some patients may succumb to secondary bacterial and fungal infections.^[21] ARDS may lead directly to respiratory failure, which is the cause of death in 70% of fatal COVID-19 cases.^[20] In addition, the vast release of cytokines by the immune system in response to the viral infection and/or secondary infections can result in a cytokine storm (CS) and symptoms of sepsis that are the cause of death in 28% of fatal COVID-19 cases.^[20] In these cases, uncontrolled inflammation inflicts multi organ damage leading to organ

failure, especially of the cardiac, hepatic, and renal systems. Most patients with SARS-CoV infection who progressed to renal failure eventually died.^[22]

IMMUNE RESPONSE TO COVID-19

The effective antiviral responses of the host innate and adaptive immunity, including the production of various pro-inflammatory cytokines, the activation of T cells, CD4, and CD8+ T cells, are essential for controlling the viral replication, limiting the spread of virus, inflammation, and cleaning the infected cells.^[11,23] Nevertheless, the tissue injury caused by the virus could induce the exaggerated production of pro-inflammatory cytokines, the recruitment of pro-inflammatory macrophages and granulocytes. This results in the CS termed as a macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH), thus leading to further tissue damage.^[24-26] Data obtained from SARS-CoV-2-infected patients have shown that severe cases may be characterized by a CS inexorably progressing to ARDS.^[14,21,27] Several features of COVID-19, such as the cytokine profile, serological markers, and clinical symptoms, resemble sHLH most commonly triggered by viral infection.^[4,25] Furthermore, important evidence is that the severity of COVID-19 is related to the level of the pro-inflammatory cytokines and subsets of immune cells.^[4,28]

COVID-19 possesses different levels of various cytokines and chemokines through the mild-to-severe stage of the disease. In SARS-CoV-2-infected patients, the retrospective analysis has demonstrated that initial plasma levels of interleukin (IL)-1 β , IL-1RA, IL-7, IL-8, IL-10, interferon (IFN)- γ , monocyte chemoattractant peptide (MCP)-1, macrophage inflammatory protein (MIP)-1A, MIP-1B, granulocyte-colony-stimulating factor (G-CSF), and tumor necrosis factor-alpha (TNF- α) are increased in patients with COVID-19. The further analysis has shown that the plasma concentrations of IL-2, IL-7, IL-17, IL-10, MCP-1, MIP-1A, and TNF- α in ICU patient are higher than non-ICU patients.^[14] Moreover, the plasma levels of IL-2, IL-6, IL-8, IL-10, and TNF- α , observed in severe infection, are prominently greater than those in non-severe infection.^[27] Few retrospective studies have revealed that the lung injury reported with Murray score is strongly associated with the level of IL-1 α , IL-1ra, IL-2, IL-7, IL-10, IL-17, IFN- γ , inducible interferon protein (IP)-10, G-CSF, and MCP-3 and these cytokines and chemokines excluding MCP-3 are positively related to SARS-CoV-2 viral load.^[28] The plasma level of IL-6, considered as a significant cytokine contributing to MAS, increases both in mild and severe patient groups of COVID-19: Severe patients have a significantly higher level of IL-6 than mild or non-severe patients.^[4,21,27,29] Furthermore, based on the assessment of pulmonary infiltration in patients with ARDS, the large area of lung injury ($\geq 50\%$) is closely correlated with the increased level of IL-6 and the subgroup of lymphocytes in the peripheral blood.^[28]

During the infection, both innate and adaptive immune cells synergistically participate in the anti-viral response.^[30] The important increment in the number of neutrophils, leukocytes, and the neutrophil-lymphocyte ratio has been observed in severe COVID-19 compared to mild cases. The prominent lymphopenia, indicating an impairment of immune system, develops in most COVID-19 patients, especially in severe ones.^[27,28] Therefore, it seems that neutrophils and leukocytes might reinforce the CS other than lymphocytes in COVID-19. The level of lymphocytes and subsets of T cells which play a significant role in the balancing of immune response varies according to the type of the virus due to possible viral pathologic mechanism. Previous investigations have elicited that the total count of lymphocytes and the subset of T cells are reduced in patients with SARS-CoV infection.^[31,32] Data from recent studies have suggested that SARS-CoV-2 infection can lead to immune dysregulation through affecting the subsets

of T cells. The significant alleviation of T cells is observed in COVID-19 and more pronounced in severe cases. In patients with COVID-19, the level of helper T cells (CD3+ and CD4+) and cytotoxic suppressor T cells (CD3+ and CD8+), and regulatory T cells are below normal level while helper T cells and regulatory T cells in severe patients are remarkably lower than non-severe patients. Regulatory T cells are responsible for the maintenance of the immune homeostasis with suppressing the activation, proliferation, and pro-inflammatory function of most lymphocytes including CD+4 T cells, CD+8 T cells, NK cells, and B cells is presented in Figure 2.^[33,34] Furthermore, the percentage of naïve helper T cells amplifies while the percentage of memory helper T cells and CD28+ cytotoxic suppressor T cells decreases in severe COVID-19.^[4,27] The equilibrium between the naïve T cells and memory T cells is fundamental for mediating the efficient immune response.^[35] In addition to T cells, the reduction of B cells and NK cells is seen in COVID-19. Another important result is the confirmed strong relationship between inflammatory markers, including ESR, CRP, and IL-6 and the subset of lymphocytes.^[27] However, previously, it has been shown that there is no significant correlation between IL-6 and subsets of lymphocytes.^[4] Although these reports have indicated that CD+4/CD+8 T cell ratio in SARS-CoV-2 infection is similar to the healthy group, the increase in this ratio and the decline of CD+8 T cells and B cells are considered as a poor predictor for the assessment of post-treatment clinical follow-up.^[4,28] Taken together, these results indicate that SARS-CoV-2 is responsible for an immune dysregulation with the induction of aberrant cytokine and chemokine response, alteration in level of the subgroup of lymphocytes all of which might result in CS and further tissue damage.

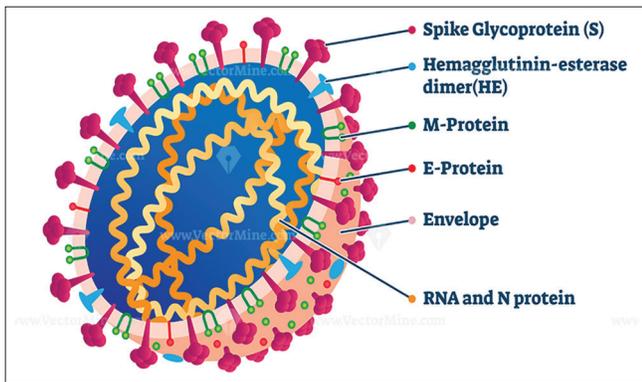


Figure 1: Structure of coronavirus

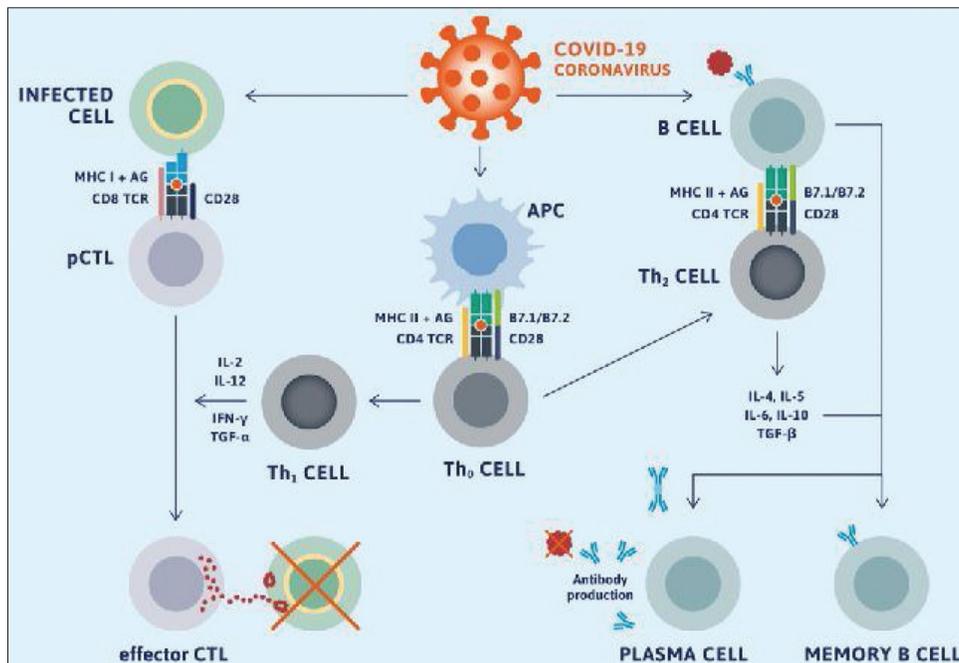


Figure 2: Adaptive immune response against coronavirus.^[36]

CONCLUSION

The effective antiviral responses of the host innate and adaptive immunity, including the production of various pro-inflammatory cytokines, the activation of T cells, CD4, and CD8+ T cells, are essential for controlling the viral replication, limiting the spread of virus, inflammation, and cleaning the infected cells. Nevertheless, the tissue injury caused by the virus could induce the exaggerated production of pro-inflammatory cytokines, the recruitment of pro-inflammatory macrophages and granulocytes. This results in the CS termed as a MAS or sHLH, thus leading to further tissue damage.

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How to cite this article: Minjibir AA, Diso SU, Nas FS, Zage AU, Ali M. Novel Coronavirus Disease-19 and Host Immune Response: A Review. *Clin Res Immunol* 2020;3(1):1-5.